REMARKS

Attached hereto is a request for an Extension of Time and the appropriate fee.

The present invention provides a system and method which can be implemented in a compact diagnostic instrument that can provide a readily accessible point of care use to thereby expand diagnostic capabilities for patients in an efficient and relatively low-cost manner.

It has been demonstrated that a particle agglutination immunoassay can be used for an infection disease related test and further, can measure CRP concentration in plasma components. Conventional requirements of separating blood into a serum or plasma with preparatory treatments before subjecting the serum to an agglutination reaction with insoluble carriers onto which antigens or antibodies are carried increases both the time and cost.

There has been a demand to provide an analyzer and method which is both accurate and efficient in quickly providing test results.

The present invention resolves this by addressing the ability of selecting a measurement wavelength that is not only free from absorption by hemoglobin but is also free from absorption by the hemoglobin reagent, e.g., saponin, etc.

To place in proper perspective the current status of the introduction of similar instrumentation in the field of hematology, recent articles such *as Performance characteristics of a point of care C-reactive protein assay* in Clinica Chimica Acta, *Performance Evaluation of the ABX Micros CRP: The First Instrument Reporting a Complete Blood Count, 3-Part Leukocyte Differential, and C-Reactive Protein Quantitation* in the Laboratory of Hematology and *Measurement of C-Reactive Protein*

by Micros CRP: Its Use in an Emergency Department in the Laboratory of Hematology are attached hereto and are referred hereto to disclose that such instruments and methodology relevant to our present invention are only now being commercially introduced.

The present invention, when compared with the traditional instrumentation, permits a quick measurement time wherein 19 separate items, including a blood corpuscle count item and CRP can be measured in under five minutes. The blood corpuscle count can be accomplished within one to two minutes.

The present invention further provides a cost reduction by shortening the time period for the separation of blood platelets, while permitting measurements to be made directly at a therapeutic location so that the results of the tests can be instantly utilized for treatment. This can free a patient from going to a hospital only for the purpose of knowing the results of the test, while still maintaining a highly accurate result. Thus, the merits of the present invention should be measured, as to its novelty and unobviousness, in view of this environment.

The new Claim 13 provides novel features of an agglutination reaction in combination with measurements taken at a wavelength free from absorption by both hemoglobin and the hemoglobin reagent.

The new Claim 16 recognizes that the sequence of hemolysis of the whole blood sample and the reaction with a latex reagent can be accomplished in either sequence, as set forth on Page 3, Lines 11-13 of our specification.

Claim 19 provides the above novel features and specifically addresses the issue raised by the Examiner of claiming approximately 800 nm.

Claim 8 was rejected as being completely anticipated by the Raffaele U.S. Patent No. 4,013,417. The Raffaele reference discloses a treatment of whole blood to permit a determination of hemoglobin in micro samples. To accomplish this purpose, whole blood was introduced into a tonometer containing a borate buffer plus a hemolysing agent. Interference filters were provided to produce wavelengths of light at 497 and 565 nm wavelengths, respectively. Another interference filter could replace one of the interference filters to provide a measuring wavelength at 620 nm.

In the determination of the total hemoglobin, the blood sample was diluted with a buffer and deoxyhemoglobin could completely be transformed into an oxyhemoglobin so that an analysis of the absorption at 497 nm could be accomplished. Methemoglobin can be measured with the interference filters set at 620 nm. Thus, the Raffaele reference fails to teach an immunoassay system and fails to teach reacting antigens in the blood to provide an agglutination reaction within soluble carriers. Additionally, there is no teaching of measuring the resultant agglutination mixture for a change in its absorption by a radiation with light of a wavelength free from absorption by both the hemoglobin and the hemolysis reagent. Thus, the Raffaele reference is not an anticipation of the present invention. The Raffaele reference rather teaches an analyzer for determining the concentration of total hemoglobin and its derivatives with clinical and physiological interests by dilution of a whole blood sample with a hemolysis reagent, measuring the absorption at a low value of 497 nm, while a buffer is kept in equilibrium with a gas having a predetermined oxygen partial pressure to avoid further oxidation.

Applicant respectfully submits that the Raffaele disclosure is neither an anticipation nor does it render obvious our present Claim 8.

Claim 8 was rejected over the Bradwell, et al. U.S. Patent No. 4,889,815 in view of the Minoru, et al. Japanese Laid Open Patent No. 7-035752 and further in view of the Hasegawa, et al. Japanese Laid Open Patent No. 6-265554.

It is clear that the Bradwell, et al. reference is easily distinguishable and does not teach nor suggest the features of the present invention. The further combination of two foreign references still fail to provide such a teaching.

> "In relying upon a foreign patent to reject a claim, the Patent Office must construe the disclosure of the foreign reference strictly, and restrict the reference to what is clearly and definitely disclosed."
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> *CITC Industries, Inc. v. Manow International Corp.*, 193 USPQ366, 368 (S.D.N.Y 1996)

The Minoru reference does not teach a lysing of whole blood with a hemolysed reagent such as saponin and further does not teach determining the concentration of a plasma component.

The Minoru, et al. reference adds purified water to a whole blood sample and heats it for 20 minutes, wherein a monoclonal antibody mixture is added to a latex suspension and heated for another 20 minutes to cause a selective agglutination reaction of latex. A sample with a known Hb AL_c value is used as a standard for performing a similar agglutination reaction in order to be able to determine the percentage of AL_c in an unknown sample. Thus, there is certainly no teaching in the Minoru, et al. reference that suggests a solution to the deficiency in the Bradwell, et al. reference.

The Hasegawa, et al. reference discloses both a method and equipment for analyzing a biochemical component of blood and suggests that in the case of a whole blood, a decision can be made by the equipment as to whether the measuring items are

applicable to the whole blood. This reference, however, does not define an irradiation at an wavelength range that is free from absorption by both hemolysis and hemolysis reagent.

Thus, it is clear that both of these secondary references fail to teach the features of the present invention as set forth in Claim 8 wherein the measuring wavelength will be free from absorption of hemolysis and hemolysis reagent.

The Office Action appears to set forth, in the last paragraph of page 5, a contention that such a suggestion can be found in Bradwell simply because a spectrometer can take measurements at or near an infrared level. This justification is a hindsight approach to fill a gap that exists in the combined teaching of the three cited references. The Office Action has already acknowledged that Bradwell, et al. does not provide any such teaching.

Claims 8-9 and 11-12 were further rejected over a combination of Bradwell, et al. in view of the Loretz U.S. Patent No. 4,357,105.

The Bradwell, et al. reference teaches using a wavelength of light in a nephelometer for analyzing the reactions of whole blood with a second detector necessary to compensate for the amount of light absorbed by hemoglobin in the sample to thereby minimizing correction for any degree of absorption as noted repetitively through the Bradwell, et al. disclosure. Thus, the Bradwell, et al. reference only discloses a wavelength range from approximately 400 to 600 nm and specifically desires such a wavelength, since the disclosure is directed to a high degree of scattering and measures light at a 90 degree position (shown in Figs. 4-7). In fact, the lysed red cells are particularly prepared so that their fragments become particles of a size which does not

scatter light in wavelengths between 460 and 510 nm. As can be determined on Col. 3, Lines 1-15, this is particularly desirable so that a high intensity light emitting diode at 480 nm could be used and thereby remove the necessity for filters. The alternative embodiments in the Bradwell disclosure (shown in Figs. 1 and 6-7) only disclose an on-axis detector that is used to time the duration of the light flash to particularly compensate for the absorption of hemoglobin. Thus, Bradwell, et al. certainly does not teach a radiation wavelength substantially free from absorption by both hemoglobin and a hemolysis reagent. The Bradwell, et al. reference also fails to teach measuring a resultant agglutination mixture for a change in its absorbance.

The Loretz reference teaches treating a prepared blood sample with a given wavelength at about 540 nm to ensure the maximum absorption in an instrument that can be relatively stabilized as far as its radiation power level output (Col. 3, Lines 16-21). Preferably, the light source is a LED with a peak wavelength of about 565 nm. Thus, the Loretz reference basically teaches a hemoglobin meter that can be accomplished with a light emitting diode operating in a wavelength of approximately 540 nm and having a filter with a cutoff of 565 nm.

The Office Action disregards the teaching of a hemoglobinometer with a solid state light emitting diode having a wavelength no longer than 553 nm and a filter with a cutoff of 560 nm and only refers to a secondary feature wherein blood turbidity testing can be accomplished by inserting an infrared source in place of the green light emitting diode. Thus, the teaching at Col. 7, Line 41 is not directed to an agglutination immunoassay system or method of quantifying a predetermined antigen in a sample of whole blood.

An objective review of the combination of these references would suggest that there is no teaching references to combine these disclosures, and the citation to a secondary feature of measuring blood turbidity is improperly sought to be incorporated into the Bradwell, et al. disclosure.

> "Most if not all inventions arise from a combination of old elements . . . Thus, every element of a claimed invention may often be found in the prior art . . . However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention . . . Rather, to establish obviousness based on a combination of elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant . . . Even when obviousness is based on a single reference, there must be a showing of a suggestion or motivation to modify the teachings of that reference . . . The motivation, suggestion or teaching may come explicitly from statements in the prior art, the knowledge of one of ordinary skill in the art, or, in some cases the nature of the problem to be solved . . ."
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> *In re Kotzab*, 55 USPQ2d, 1313 (Fed. Cir. 2000)

Claims 8-9 and 11-12 were rejected over the Bradwell, et al. reference in view of the Osten, et al. U.S. Patent No. 5,729,333. The Osten, et al. reference was based upon a recognition that a hematocrit in whole blood was found to have a suitable direct mathematical correlation to the concentration of hemoglobin provided that the blood has few or no lysed erythrocytes. The Osten reference further noted in Col. 3, Lines 7-11, as follows which teaches away from the obviousness of 800 nm:

> "Moreover, the choice of specific wavelengths in near-infrared spectra for which whole blood samples may be best monitored is not straightfoward due to variances in the broad peaks of water and various forms of hemoglobin in such NIR spectra."
>
> (underline added)

As noted in Col. 4, in the case of a hemoglobin concentration determination through a mathematical regression analysis, Loretz sought a wavelength range of 1150 to 1190 nm. Thus, the Osten reference can characterize properties of biological matter containing water by analyzing them in with an absorbance peak around 1150 to 1190 nm. Again, the Osten reference does not provide any teaching to suggest such a drastic modification of the Bradwell, et al. reference nor does it teach 800 nm.

It is apparent that the only teaching reference is a desire to combine diverse references and the result of the zeal of examination, and such references are only combined in hindsight from the teachings of the present application. Certainly, neither of these references teach an agglutination immunoassay method as set forth in the presently pending claims.

In summary, none of the references alone or in combination teaches the features of the present invention wherein an agglutination immunoassay method and system of treating whole blood and selecting an appropriate wavelength to measure the resulting reaction products while voiding absorption from hemoglobin and hemolysed reagent is accomplished. By adopting these procedures, a highly efficient instrument and method can be utilized to provide quick and accurate readings to assist in patient care without requiring an extensive laboratory facility and the pre-preparation of whole blood samples.

By providing these advantages, applicant has provided a significant contribution that is worthy of receiving patent protection.

If the Examiner believes a telephone interview will help further the prosecution of this case, she is respectfully requested to contact the undersigned attorney at the listed telephone number.

I hereby certify that this correspondence is being sent First Class Mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231 on October 25, 2002.

By: Candy Neu

Signature

Date: October 25, 2002

Respectfully submitted,

SNELL & WILMER

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